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Diagnostic approaches for immunocompromised paediatric patients with pulmonary infiltrates

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ABSTRACT

Pulmonary infiltrates in immunocompromised children often pose problems in terms of deciding on further diagnostic and therapeutic procedures, but few studies have evaluated the value of non-invasive and invasive diagnostic methods in paediatric populations. Both galactomannan ELISA and PCR protocols appear to be less useful in children than in adults. Invasive procedures, such as bronchoalveolar lavage or lung biopsy, can yield a pathohistological diagnosis and/or the isolation of a pathogen. Prospective studies in paediatric patients are needed urgently to assess the value of different diagnostic procedures and to define an effective and safe diagnostic strategy for the individual child.

Keywords Aspergillosis, biopsy, bronchoalveolar lavage, children, diagnosis, immunosuppression, pulmonary infiltrate

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Pulmonary infiltrates revealed by conventional chest roentgenograms or computerised tomography (CT) scans often pose problems in terms of deciding on further diagnostic and therapeutic procedures, particularly in immunocompromised children [1]. Differential diagnoses include infections caused by a variety of bacteria and fungi, metastases of an underlying malignancy, or lesions induced by previous therapy [2,3]; however, a precise diagnosis is essential for an appropriate therapeutic approach. In a survey of 27 paediatric cancer centres, we found that non-invasive and invasive diagnostic procedures were performed regularly in immunocompromised children with pulmonary infiltrates by only 18 and nine centres, respectively. Reasons given for the low usage of these procedures included the risk of adverse events with invasive modalities, and the high sensitivity and specificity of imaging studies. However, a retrospective radiological study [4] of 27 children with documented aspergillosis failed to find a halo-sign indicative of invasive aspergillosis, but documented various other findings, including segmental and multilobar consolidation, perihilar infiltrates, multiple small nodules and larger peripheral nodular masses. This might reflect the relatively late stage of disease during which the patients were scanned, since the halo-sign is seen in up to 75% of adult patients within the first 96 h, compared with only 20% of adult patients on day 14 [5]. It has been suggested that there is a spectrum of radiological disease presentations in paediatric patients with pulmonary aspergillosis that is related directly to age [6]. Importantly, CT scans of immunocompromised children with fungal disease may mimic a variety of diseases, including malignant tumour [3]. To date, no study has evaluated the value of magnetic resonance imaging (MRI) in children with cancer. This method does not expose the patient to radiation, but is hampered by the need for sedation of young children. Similarly, the role of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) as a diagnostic tool to detect infection in patients with cancer is unclear [7].

In patients with pulmonary infiltrates, a causative pathogen can rarely be isolated from blood cultures [8,9]. In recent years, progress has been made in the development and evaluation of non-invasive diagnostic assays for the detection of bacterial or fungal antigens and genomic DNA sequences [9]. An ELISA detecting galactomannan (GM), a component of the *Aspergillus* cell wall [10], can be used with samples such as blood, cerebrospinal and bronchial fluid, but the sensi-

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tivity and specificity of this test vary considerably according to the patient population and the cut-off level used [11,12]. A study of 3294 serum samples from 797 episodes, of which 153 had been classified previously as invasive aspergillosis (31 definite, 67 probable, 55 possible) [11], found that the manufacturer's recommendation of a positive cut-off level of >1.5 resulted in sensitivities of 64.5%, 16.4% and 25.5% in definite, probable and possible episodes of invasive aspergillosis, respectively. The overall specificity was 94.8%, but this was significantly lower (47.6%; $p < 0.0001$) for the 42 children analysed. This might reflect the predominantly milk-based diet of children, as GM is present in milk and may translocate across an intestinal wall that has been damaged by chemotherapy-induced mucositis. Furthermore, lipoglycan from *Bifidobacterium bifidum* [13], as well as drugs of fungal origin, e.g., piperacillin-tazobactam, may cause elevated GM levels [14]. On the other hand, anti-*Aspergillus* antibodies [11], or the use of antifungal prophylaxis or empirical treatment [12], may cause false-negative results.

PCR offers the potential for rapid and sensitive diagnosis of invasive fungal infection, and might allow quantification of fungal loads. In an animal model of invasive pulmonary aspergillosis, 15 of 60 blood samples yielded a positive PCR result, but no pathogen could be isolated from the blood culture [15]. There are various different PCR protocols, but a commercially available PCR assay is still lacking. In addition, there are problems in knowing how to interpret PCR-positive culture-negative results, which could reflect either contamination or sub-clinical infection masked by empirical therapy or neutrophil recovery. A retrospective study of 20 children and 21 adults with invasive aspergillosis suggested that a serum-based Taqman real-time PCR assay was more specific than GM ELISA, and that a combination of the two could improve the accuracy of the diagnosis [16]. It remained unclear why the sensitivity of the PCR was lower in children compared with adults.

In contrast to serological and molecular methods, invasive modalities such as bronchoalveolar lavage (BAL) or biopsy can yield a pathohistological diagnosis and/or the isolation of a pathogen. In a study of 53 children with cancer, BAL was performed because of fever and/or abnormalities seen on chest radiograph. A pathogen was isolated from 15 of these 53 children, and malignant cells were found in one patient; however, minor complications related to the diagnostic procedure occurred with 16 patients [17]. Concomitant to BAL, trans-bronchial biopsy (TBB) can be performed during bronchoscopy, even in very small children if special techniques are used [18]. Complications such as pneumothorax or bleeding are rare. A study using TBB reported an overall complication rate of 2% among 84 paediatric patients [19]. All complications occurred with patients in whom biopsies were performed with adult forceps. Unfortunately, use of the smaller bronchoscope forceps resulted in a lower yield of adequate tissue compared with the adult biopsy forceps (85% vs. 95%) [19]. As an alternative, trans-thoracal bronchoscopy (TTB) might be an accurate and safe option in children with small pulmonary nodules [20,21]. Cahill *et al*. [21] described 64 paediatric patients who underwent TTB, mostly for suspected malignancy ($n = 24$) or infection ($n = 36$). The overall diagnostic yield was 91%, and only one patient suffered from tension pneumothorax. Importantly, serological and molecular methods can also be used with specimens obtained by invasive procedures. For example, PCR assays detecting fungal infection have been used successfully with BAL specimens obtained from patients with pulmonary aspergillosis [22], but there is an absence of definitive data for paediatric patients.

Whereas TBB and TTB are hampered by small sample volumes, especially with children, open lung biopsy (OLB) can reveal typical macroscopic changes, and may provide adequate tissue samples for pathological examination and the culture of pathogens. Disadvantages are the need for general anaesthesia and the risk of bleeding. An analysis of 17 immunocompromised children revealed that OLB yielded the correct diagnosis with nine patients for whom examination of blood, sputum and BAL had not been informative [23]. If OLB is being considered, it should not be delayed, as morbidity and mortality rates are significantly lower for children without respiratory failure, compared with children with respiratory failure (14% and 0% vs. 65% and 38%, respectively) [24].

Although it is unclear whether greater diagnostic accuracy improves the overall outcome, a better diagnostic approach might ultimately

improve therapeutic strategies, including the development of new drugs and immunotherapeutic approaches. However, even invasive diagnostic procedures seem to be associated with a low incidence of adverse events, and there has to be a balance between the risk of complications and the benefits of improved diagnosis. To this end, prospective studies are required urgently in paediatric patients to assess the value of the different diagnostic procedures and to define a safe and cost-effective diagnostic strategy for the individual patient.

REFERENCES

1. Groll AH, Irwin RS, Lee JW, Pizzo PA, Walsh TJ. Management of specific infectious complications in children with leukemias and lymphomas. In: Patrick CC, ed. *Clinical management of infections in immunocompromised infants and children*. Philadelphia: Lippincott Williams & Wilkins 2001; 111–143.
2. Park KJ, Chung JY, Chun MS, Suh JH. Radiation-induced lung disease and the impact of radiation methods on imaging features. *Radiographics* 2000; **20**: 83–98.
3. de Camargo B, Pereira de Carvalho Filho N, Lopes Pinto CA, Werneck da Cunha I, de Pinho ML. Cryptococcosis mimicking a pulmonary metastasis in a child with Wilms tumor. *Med Pediatr Oncol* 2003; **41**: 88–89.
4. Thomas KE, Owens CM, Veys PA, Novelli V, Costoli V. The radiological spectrum of invasive aspergillosis in children: a 10-year review. *Pediatr Radiol* 2003; **33**: 453–460.
5. Caillot D, Couaillier JF, Bernard A *et al.* Increasing volume and changing characteristics of invasive pulmonary aspergillosis on sequential thoracic computed tomography scans in patients with neutropenia. *J Clin Oncol* 2001; **19**: 253–259.
6. Steinbach WJ. Pediatric aspergillosis: disease and treatment differences in children. *Pediatr Infect Dis J* 2005; **24**: 358–364.
7. Miceli MH, Jones Jackson LB, Walker RC *et al.* Diagnosis of infection of implantable central venous catheters by [18F]fluorodeoxyglucose positron emission tomography. *Nucl Med Commun* 2004; **25**: 813–818.
8. Lehrnbecher T, Varwig D, Kaiser J *et al.* Infectious complications in pediatric acute myeloid leukemia: analysis of the prospective multi-institutional clinical trial AML-BFM 93. *Leukemia* 2004; **18**: 72–77.
9. Peters RP, van Agtmael MA, Danner SA, Savelkoul PH, Vandenbroucke-Grauls CM. New developments in the diagnosis of bloodstream infections. *Lancet Infect Dis* 2004; **4**: 751–760.
10. Mennink-Kersten MA, Donnelly JP, Verweij PE. Detection of circulating galactomannan for the diagnosis and management of invasive aspergillosis. *Lancet Infect Dis* 2004; **4**: 349–357.
11. Herbrecht R, Letscher-Bru V, Oprea C *et al. Aspergillus* galactomannan detection in the diagnosis of invasive aspergillosis in cancer patients. *J Clin Oncol* 2002; **20**: 1898–1906.
12. Marr KA, Balajee SA, McLaughlin L *et al.* Detection of galactomannan antigenemia by enzyme immunoassay for the diagnosis of invasive aspergillosis: variables that affect performance. *J Infect Dis* 2004; **190**: 641–649.
13. Mennink-Kersten MA, Ruegebrink D, Klont RR *et al.* Bifidobacterial lipoglycan as a new cause for false-positive platelia *Aspergillus* enzyme-linked immunosorbent assay reactivity. *J Clin Microbiol* 2005; **43**: 3925–3931.
14. Viscoli C, Machetti M, Cappellano P *et al.* False-positive galactomannan platelia *Aspergillus* test results for patients receiving piperacillin-tazobactam. *Clin Infect Dis* 2004; **38**: 913–916.
15. Loeffler J, Kloepfer K, Hebart H *et al.* Polymerase chain reaction detection of *Aspergillus* DNA in experimental models of invasive aspergillosis. *J Infect Dis* 2002; **185**: 1203–1206.
16. Challier S, Boyer S, Abachin E, Berche P. Development of a serum-based Taqman real-time PCR assay for diagnosis of invasive aspergillosis. *J Clin Microbiol* 2004; **42**: 844–846.
17. Park JR, Fogarty S, Brogan TV. Clinical utility of bronchoalveolar lavage in pediatric cancer patients. *Med Pediatr Oncol* 2002; **39**: 175–180.
18. Mullins D, Livne M, Mallory GB Jr, Kemp JS. A new technique for transbronchial biopsy in infants and small children. *Pediatr Pulmonol* 1995; **20**: 253–257.
19. Visner GA, Faro A, Zander DS. Role of transbronchial biopsies in pediatric lung diseases. *Chest* 2004; **126**: 273–280.
20. Connolly BL, Chait PG, Duncan DS, Taylor G. CT-guided percutaneous needle biopsy of small lung nodules in children. *Pediatr Radiol* 1999; **29**: 342–346.
21. Cahill AM, Baskin KM, Kaye RD, Fitz CR, Towbin RB. CT-guided percutaneous lung biopsy in children. *J Vasc Interv Radiol* 2004; **15**: 955–960.
22. Buchheidt D, Baust C, Skladny H *et al.* Clinical evaluation of a polymerase chain reaction assay to detect *Aspergillus* species in bronchoalveolar lavage samples of neutropenic patients. *Br J Haematol* 2002; **116**: 803–811.
23. Steinberg R, Freud E, Ben-Ari J *et al.* Open lung biopsy – successful diagnostic tool with therapeutic implication in the critically ill paediatric population. *Acta Paediatr* 1998; **87**: 945–948.
24. Davies L, Dolgin S, Kattan M. Morbidity and mortality of open lung biopsy in children. *Pediatrics* 1997; **99**: 660–664.